INCIDENCE OF HYPERTENSION IN ASTHMA PATIENTS WHO TREATED WITH BETA-2 AGONISTS BRONCHODILATORS

by Aprilita Rina Yanti Eff

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 9, Issue 4, 2017

Original Article

INCIDENCE OF HYPERTENSION IN ASTHMA PATIENTS WHO TREATED WITH BETA-2 AGONISTS BRONCHODILATORS

APRILITA RINA YANTI EFF

Departement of Public Health, Faculty of Health Sciences Esa Unggul University, Jakarta-Indonesia
Email: aprilita.rinayanti@esaunggul.ac.id

Received: 10 Jan 2017 Revised and Accepted: 27 Feb 2017

ABSTRACT

Objective: To determine the prevalence of hypertension in hospitalized patients with asthma who were treated with beta-2 agonists. To evaluate the correlation between the duration of the use of beta-2 agonist with the incidence of hypertension.

Methods: This research is a descriptive epidemiological, observational cross-sectional and retrospective study design. The study population was all adult asthma patients (age ≥ 25) without a concomitant diseases such as hypertension or metabolic syndrome treated with β2 agonists as a bronchodilator and underwent hospitalized in January 2015-December 2015 (n=108). Patient data were collected from the medical record. Data were analyzed using univariate and bivariate to count the number of occurrences of hypertension and recognizing the correlation between the duration of the use of β2 agonists with hypertension event.

Results: The incidence of hypertension in patients with asthma who were treated with beta-2 agonists are 50, 93% at the stage of pre-hypertension (120 mm Hg/80 mm Hg) and 25, 9% in stage I hypertension (140 mmHg/90 mmHg). Body weight and duration of therapy with a β2 agonist positively correlated with the incidence of hypertension with a correlation coefficient (r) 0.231 and 0.386 respectively.

Conclusion: In this study, duration of therapy with a β2 agonist in asthma patients positively correlated with the incidence of hypertension.

Keywords: Incidence of hypertension, Asthma patients, Bronchodilators, β2 agonists

DOI: http://dx.doi.org/10.22159/ijpps.2017v9i4.17013

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways. Asthma is a very common disease that involves complex interactions between environmental factors, airway obstruction, bronchial hyper responsive, and inflammation. The main picture dominant cause clinical symptoms is smooth muscle contraction and inflammation that cause shortness of breath, coughing, wheezing or chest tightness. Asthma can be triggered by various factors such as allergic responses, respiratory infections, excessive physical exercise, irritation of the respiratory tract and the use of anti-inflammatory drugs that can cause airway obstruction, and bronchoconstriction [1].

Mast cells, eosinophils and T-lymphocytes are important mediator in causing asthma. In sensitive individuals, inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or early morning. Symptoms of respiratory tract obstruction may be reversible spontaneously or with treatment [2].

The prevalence of asthma in each country is different and is associated with changes in lifestyle. The increase in the prevalence of asthma in the last 40 y is closely related to the increased incidence of allergies [3]. Several studies in Asia indicate that the increase in the prevalence of asthma by age. The prevalence in the Asian population is 5% lower than in Europe, while in Asia the prevalence of asthma in the elderly is 1.3-15.3%. Temporal trends in prevalence exhibited the recent increase of adult asthma in Hongkong, Japan, and Korea [4]. Asthma in adults often resulted in worsening of lung function and limited air flow. Early diagnosis can reduce the rate of decline in lung function immediately. It is estimated that the incidence of asthma in the population was 4.6 cases per 1,000 person-years in women and 3.6 in men, and there is a tendency of higher incidence with age [5].

Management of asthma is not only intended to relieve symptoms of shortness of breath but also normalizes pulmonary function and minimize the symptoms of asthma, minimizing the occurrence of attacks, reduce the use of a bronchodilator and minimize drug side effects. The goals for successful management of asthma are attained and keep control of asthma symptoms, preserve in normal activity levels, including exercise, maintain pulmonary function as close to normal as possible prevent asthma exacerbations, avoid adverse effects from asthma medications and prevent asthma mortality [6].

Asthma can be controlled and maintained by proper medication. Several ways can be used to control asthma, such as to avoid trigger factors and environmental factors causing asthma, help the patients to be able to manage and overcome asthma themselves [7]. The efforts to control asthma attacks carried out using non-pharmacological and pharmacological therapy. There are two types of drugs commonly used that quick-relief and long-term control. These medications include short-acting beta agonists (SABAs), anticholinergics, and systemic corticosteroids, which speed recovery from acute exacerbations. Long-term control medications include inhaled corticosteroids, long-acting beta-agonists (LABAs), long-acting anticholinergic, combination inhaled corticosteroids and long-acting beta agonists, methylxanthines, and leukotriene receptor antagonists [8].

Beta-2 agonists relieve bronchospasm by relaxing the smooth muscles of the bronchi. These agents act as bronchodilators and are used to treat bronchospasm in acute asthma episodes and to prevent bronchospasm associated with exercise-induced asthma or nocturnal asthma [9]. β-2 agonist is strong bronchodilator, and effective in the treatment of asthma due to beta-2 agonists play a role in dilating the smooth muscle of the bronchus. Stimulation β-2 adrenergic receptor activates adenylate cyclase, resulting in increased intracellular AMP cyclic and relaxation of smooth muscle [10].

The use of bronchodilators of the β-2 agonist class can cause adverse effects on the cardiovascular, elevated blood pressure, tremor, palpitations, tachycardia, and headache, especially in the elderly and patients with the preexisting cardiac disease. A study conducted by Macie *et al.*, 2008 showed that there is a relationship between the uses of β-2 agonist with cardiovascular morbidity [11].

The presence of β-2 receptors on the heart may explain why the class of drugs β-2 can cause side effects on the heart and cardiovascular. A study conducted by Lemaitre *et al.*, 2002 showed

that asthma patients who were treated with β-2 agonists in the form of metered dose or nebulized lead to cardiac arrest. The risk of myocardial infarction 7-fold greater in patients with a history of cardiovascular disease [12]. Meta-analysis study of the use of β2 agonist in patients with constriction of the airways showed that the use of a single β-2 agonist may increase the heart rate by 9.12 bpm and low plasma potassium concentration of 0.36 mmol/l. Mild tachycardia occurs when patients first exposed to β2 agonist. Tachycardia can lead to decreased venous return flow, activates the sympathetic nervous system, improve the cardiotonic and inotropic effect. β2 agonist also stimulates β-2 receptors in the heart, which increases heart rate and blood pressure directly [11, 12].

Persahabatan Hospital is a referral hospital where the lung and respiratory diseases including asthma patients. This study was conducted to assess the incidence of hypertension in asthma patients who were treated with β2 agonists at Persahabatan hospital. In this study, we determined the relationship of incidence hypertension and using B2 agonist.

MATERIALS AND METHODS

Methods

This research is a descriptive epidemiological, observational cross-sectional and retrospective study design. The study population was all adult asthma patients (age ≥ 25) without a concomitant disease such as hypertension or metabolic syndrome treated with β2 agonist as a bronchodilator and underwent hospitalized in January 2015-December 2015 (n=108). This study was conducted after approval of the Institutional Ethics Committee with approval number 560/ETIK/2016. Patient data were collected from the medical record. The data include patient general data, such as gender, body weight and age; history of previous disease, the patient complained during hospitalized, diagnosis, laboratory examinations and vital sign, and drugs received by patients. Data were analyzed using univariate and bivariate to count the number of occurrences of hypertension and recognizing the correlation between the duration of the use of β2 agonists with hypertension event.

RESULTS

Asthma patient's profile who were hospitalized

a. Number of patients

Patients who were hospitalized from January 2015 through December 2015 were 380 and the number of patients aged ≥ 25 y as many as 292 people. Patients who met the inclusion criteria were 108 people.

b. Patient's age

Patient's classification by age can be seen in fig. 1. From fig. 1 it appears that distribution of age the patients were 25->81 y, with the largest distribution in the age of 51-60 y.

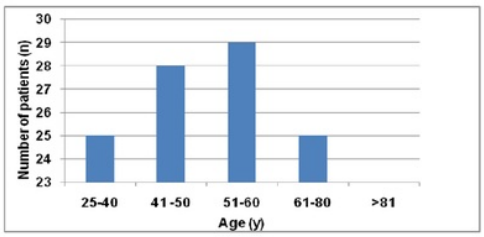

Fig. 1: Patients classification by age

c. Patients classification by sex

From the data, it appears that a number of female patients as much as 77 (71.29%) were higher than male patients as many as 31 people (28.70%).

d. Patients classification by body weight

The patients' weight were distributed between 41 kg-60 kg with the highest number was 87 (80.55%). Classification of the patient's weight can be seen in fig. 2.

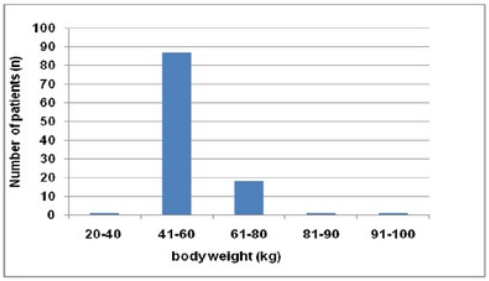

Fig. 2: Patients classification by body weight

e. Laboratory data

From the observation of laboratory data, 5 patients showed enhanced the value of leukocytes above normal, and 103 patients showed normal laboratory values.

f. Duration of therapy

The duration of treated patients is presented in fig. 3. The duration of therapy adjusted to the condition and the level of patients' recovery. From table 4 it shows that the number of patients were treated for 1-5 d as many 44 (40.74%), 6-10 d as many 42 (38.88%), 11-20 d as many 21 d (19.44%), and 21-30 d numbered 1 person (0.90%).

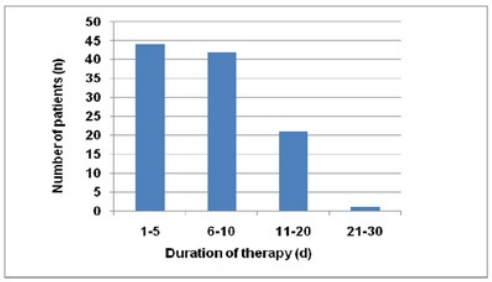

Fig. 3: Patients classification by duration of therapy

g. Classification of hypertension

The observation of blood pressure in asthma patients who were treated with beta-2 agonists can be seen in table 1.

Table 1: Patients classification by hypertension category

Hypertension category (SBP/DBP)	Number of patients (n)	Percent (%)
Normal (<120 mmHg/<80 mm Hg)	25	23.50
Pre hypertension (120 mm Hg/80 mm Hg)	55	50,93
Stage I hypertension (140 mmHg/90 mmHg)	28	25,90
Stage II hypertension (>160 mm Hg/≥ 100 mm Hg)	0	
Total	108	100

h. Type drugs used

Type drugs used adjusted to the patient's condition. The types of drugs used can be seen in table 2

Table 2: Type drugs used

Bronchodilators (Methyl xanthin)	Beta 2 agonist	Corticosteroids	Antibiotics	Other drugs
Aminophylin	Ventolin inhaler (Salbutamol)	Methyl Prednisolone	Azitromicyn	Ranitidin
Theophylin	Bricasma (Terbutalin sulfate)	Medixon	Levofloxacin	Black cough medicine
	Salmoterol	Obucort (Budesonide)	Cefixime	Cetrizin
	Formoterol		Cetriaxon	Mefenemic acid
	Combivent inhaler			Ambroxol
				Omeprazol

DISCUSSION

Asthma as a chronic inflammatory disorder of the airways that is accompanied by the role of various cells, in particular, mast cells, eosinophils, and T lymphocytes. In susceptible people, this inflammation causes recurrent episodes of wheezing, breathlessness, chest distress taste, and coughing, particularly at night or early day [7]. Asthma is caused by many factors, where the onset of age plays an important role. Although much of the literature states that the majority of asthma in children, but the incidence of asthma that occur during adulthood different to the incidence of asthma that began in childhood. Asthma in adults is often nonatopic and patients have a poor prognosis because of decline in lung function rapidly and limited of breathing [5]. Genetic predisposition, family history of allergy and asthma, viral respiratory infections, bacterial colonization, allergic sensitization and tobacco exposure are the main risk factors associated with childhood-onset asthma [13].

The national prevalence rate of asthma by basic medical research shows that people with asthma are more common in the age of 61-80 y [14], while based on the results of data from Persahabatan Hospital patients 51-60 y old is the most who suffer from asthma. This is due to differences in study populations; physical activity increased sensitivity or allergy and a decline in lung function. Allergy is one of the factors that play a role in asthma and asthma severity. According to reports from the UK, in children aged 16 y with a history of asthma or wheezing, wheezing attacks will happen twice as much if they have experienced hay fever, allergic rhinitis or eczema [15]. Statistical test results indicate the absence of correlation relationship between patient's age and the incidence of hypertension in this study, although a study conducted by Humayaun et al., 2009 showed that hypertension is strongly related to age and gender [16]. The increase in age, atherosclerotic and calcification will change arterial and arteriolar stiffness that cause elevated blood pressure [17].

From table 1 it can be seen that women asthma patients were higher (77/71.29%) than men (31/28.70%). Statistical test results showed that no correlation between gender and the incidence of hypertension even though in theory, gender is one of the risk factors of hypertension and more men suffer from hypertension than women due to the influence of lifestyle and hormonal factors. A study conducted by Jaakkola et al., 2003 also showed that people with asthma more women (76.6%) than men (23.4%) [18]. Dyspnea and asthma symptoms correlated with gender because women have a higher risk for experiencing anxiety or depression throughout their lives [19]. The concentration of leptin in women is higher than men. The serum concentration of leptin in females was positively related to estrogen and stimulation of the ob-gene will release leptin and increases serum leptin [20]. Leptin is a neuroendocrine hormone that plays in managing food intake, metabolism, and fat accumulation. Leptin also influences blood pressure and redound to hypertension by way of sympathetic activation in the vasculature or at the renal level [21].

Hormonal factors affect respiratory health and disease along with a woman's life. Menstrual cycle phase affects bronchial hyper-responsiveness, respiratory symptoms and asthma. Estrogen receptors are discovered on both vascular endothelial and smooth muscle cells and important in the pathogenesis of asthma and allergy when exposed to the hormone. Estrogen and progesterone receptors also are found on mast cells in the airways. β-estradiol and progesterone degranulated mast cells significantly as characteristic of an allergic reaction. Hormone replacement therapy in postmenopausal women seems to be related to the incidence of asthma [22, 23]. A Study by Troisi et al. proved that postmenopausal women who were never users of replacement hormones had a significantly lower age-adjusted risk of asthma than premenopausal women [24].

Body weight is one of the risk factors in asthma. Obesity is marked by low levels of systemic inflammation with elevated levels of inflammatory cytokines, adipokines, and acute phase proteins, including Leptin, Interleukin-6 (IL-6), tumor necrosis factor- (TNF), and C-reactive protein (CRP) [25]. Obesity leads higher oxygen cost of breathing caused dyspnea due to decreased compliance of excess weight pressing on the chest wall, fatty infiltrates from the chest wall, and increased blood volume [26]. Expression some of pro-inflammatory molecules such as TNF , IL-6, transforming growth factor β1 (TGF β1), and CRP in adipose tissue of obese people looked overlaps with the immune function of adipocytes and macrophages of T lymphocytes, particularly with regard to the elaboration of inflammatory cytokines [27]. CRP has an important role in immune defence mechanisms that will interacting with the complement system [28]. From fig. 2 is seen that a patient's weight ranged from 20 kg-100 kg, but the weight 41 kg-60 kg much more ie 87 people (80.55%), this was due to of differences in activity, diet, and work. Statistical test results showed that there is a positive correlation between body weight with hypertension (r=0. 231).

Duration of therapy in asthma patients adjusted on health conditions and the degree of patients' recovery. From fig. 3 is seen that the duration of therapy that is 1-5 d (40.74%), 6-10 d (38, 8%), 11-20 d (19, 4%) and 21-30 d. Data shows that the duration of therapy in patients with asthma is not more than one month. Statistical test results showed that the correlation between duration of therapy with hypertension.

Asthma patients are treated based on the severity of their disease. To overcome shortness of breath, patients treated with β2 agonists such as salbutamol, terbutaline or formoterol either inhalation or tablets with a dosage as inhalation 3 times to 6 times daily and administered β2 agonist orally starting at 1 daily, up to 3 times daily or according to the conditions of patients and severity of the disease. Long-acting β2 agonist is a drug of choice in the treatment of asthma to increase control symptoms. Inhaled β2-adrenoceptor (β2-AR) agonist is an important bronchodilator drug in the treatment of bronchial asthma, both as a symptom relievers and, in combination with inhaled corticosteroids, as disease control [29]. Beta 2 agonist is preventing bronchoconstriction induced by various stimuli excitatory airway mediators. Asthma is a disease that occurs due to inflammation of the airways so that asthma therapy involves the use of anti-inflammatory agents and bronchodilators. When used in inhalation and inhaled into the lungs, β2-adrenoceptor agonist bronchodilators give rapid and effective reversal of acute airway obstruction caused by bronchoconstriction, with minimal acute adverse effects in patients [30]. β2 agonist receptors besides being able to relax smooth muscle airways also play a role in providing protection against allergen-induced asthmatic reactions. In asthma, airway smooth muscle cells play a role in the release of

inflammatory mediators such as prostanoid and chemokines that can immortalize and amplify the inflammatory process in the airways. Short and long-acting β2 agonist can reduce the expression of the surface intercellular adhesion molecule-1 and release of granulocyte-macrophage colony stimulating factors induced by interleukin-1β in airways smooth muscle [31]. A study conducted by Macie *et al.*, 2008 shows that there is a relationship between the uses of β2 agonist with cardiovascular morbidity [11]. The most common side effects caused by the use of β2 adrenoceptor agonist-mediated through β2 adrenoceptor, which is a tremor in skeletal muscle, cardiac effects, metabolic changes including hyperglycemia, hypokalemia and decreased partial pressure of arterial oxygen (PaO_2). This effect occurs both in healthy volunteers and asthma patients [30]. Lemaitre *et al.* showed that use of inhaled β2 agonists increases heart attack risk 2-fold (odds ratio main [OR] = 1.9; 95% confidence interval [CI]: 1.1-3.3) among patients with asthma, but not among those with COPD (OR) =1,3;95% CI: 0.6 to 2.7), after adjusting for risk factors [12].

Giving β2 agonists can cause hypertension because these drugs in addition to influencing β2 receptors also affect β1 receptors in the heart, which results in positive inotropic effects and positive chronotopic with the final result of the increase in blood pressure [32]. From table 5 it is seen that besides getting β2 agonist as bronchodilators, patients also get other drugs such as Aminophylline, Theophylline and cough medicine (ambroxol, Mucopect). Some patients also get medicine to treat stomach ulcers such as antacids, omeprazole and inpepsa syrup and patients with laboratory test results show an increase in leukocyte administered antibiotics orally or injections such as ceftriaxone and azithromycin. From the laboratory data showed 5 patients experienced an increase in leukocyte above normal. While on the other laboratory parameters such as neutrophils, lymphocytes, monocytes, eosinophils, basophils, sodium, potassium, chloride, urea and creatinine in the normal value.

CONCLUSION

The incidence of hypertension in patients with asthma who were treated with beta-2 agonists are 50, 93% at the stage of pre-hypertension (120 mm Hg/80 mm Hg) and 25, 9% in stage I hypertension (140 mmHg/90 mmHg). Body weight and duration of therapy with a β2 agonist positively correlated with the incidence of hypertension with a correlation coefficient (r) 0.231 and 0.386 respectively.

CONFLICTS OF INTERESTS

Declared none

REFERENCES

1. Female SK, Turapati PR, Sridhar R, Ponugoti RAO. Asthma: alternative management approaches. Asian J Pharm Clin Res 2011;4:1–6.
2. Baky AA. Inflammation in asthma. Egypt J Pediatr Allergy Immunol 2003;1:68–70.
3. Epidemiology of Asthma: Prevalence and Burden of Disease: Masoli M, Fabian D, Holt S, Beasant S. In: Brasier AR. editors. Heterogeneity in asthma, advances in experimental medicine and biology. New York: Springer Science+Business Media; 2014. p. 17-21.
4. Song WJ, Kang MG, Chang YS, Cho SH. Epidemiology of adult asthma in Asia: toward a better understanding. Asian Pac J Allergy Immunol 2014;4:75–85.
5. de Nijs SB, Venekamp LN, Bel EH. Adult-onset asthma: Is it really different? Eur Respir Rev 2013;22:44–52.
6. GINA. Pocket Guide for asthma management and prevention. Glob Initiat Asthma; 2015. p. 32.
7. Fitzgerald JM, Levy ML. Global strategy for asthma management and prevention (2015 update). Glob Strateg Asthma Manag Prev; 2015.
8. Zdanowicz MM. Teachers topics pharmacotherapy of asthma. Am J Pharm Educ 2007;71:1–12.
9. Morris J. Asthma medication. Medscape; 2016. Available from: http://emedicine.medscape.com/article/296301-treatment. [Last accessed on 26 Oct 2016]
10. Barisione G, Baroffio M, Crimi E, Brusasco V. Beta-adrenergic agonists. Pharmaceuticals 2010;3:1016–44.
11. Macie C, Wooldrage K, Manfreda J, Anthonisen N. Cardiovascular morbidity and the use of inhaled broncho-dilators. Int J COPD 2008;3:163–9.
12. Lemaitre RN, Siscovick DS, Psaty BM, Pearce RM, Raghunathan TE, Whitsel EA, *et al.* Inhaled beta-2 adrenergic receptor agonists and primary cardiac arrest. Am J Med 2002;113:711–6.
13. Bisgaard H, Bonnelykke K. Long-term studies of the natural history of asthma in childhood. J Allergy Clin Immunol 2010;126:187–97.
14. Indonesia Health Ministry. Basic health research. Indonesia Research and Health Development agency; 2014. p. 87.
15. Network GA. The global asthma report 2014. Available from: http://www.globalasthmanetwork.org/ [Last accessed on 26 Oct 2016]
16. Humayun A, Shah AS, Sultana R. Relation of hypertension with body mass index and age in a male and female population of Peshawar. Pakistan J Ayub Med Coll Abbottabad 2009;21:63–5.
17. Pinto E. Blood pressure and ageing. Postgrad Med J 2007;83:109–14.
18. Jaakkola MS, Piipari R, Jaakkola N, Jaakkola JJ. Environmental tobacco smoke and adult-onset asthma: a population-based incident case-control study. Am J Public Health 2003;93:2055–60.
19. Nowobilski R, Furgał M, Polczyk R, de Barbaro B, Szczeklik A. Gender gap in psychogenic factors may affect the perception of asthma symptoms. J Investig Allerg Clin Immunol 2011;21:193–8.
20. Vayghan HJ, Esfanjani AT, Mameghani ME. Sex differences in serum leptin and adiponectin levels in apparently healthy Iranian adults. Int Res J Appl Basic Sci 2013;4:3099–103.
21. Khokhar KK, Sidhu S, Kaur G. Correlation between leptin level and hypertension in normal and obese pre-and postmenopausal women. Eur J Endocrinol 2010;163:873–8.
22. Macsali F, Svanes C, Bjørge L, Omenaas ER, Real FG. Respiratory health in women: from menarche to menopause. Expert Rev Respir Med 2012;6:187–202.
23. Bellia V, Augugliaro G. Asthma and menopause. Monaldi Arch Chest Dis 2007;67:125–7.
24. Troisi RJ, Speizer FE, Willett WC, Trichopoulos D, Rosner B. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma–a prospective cohort study. Am J Respir Crit Care Med 1995;152:1183–8.
25. Shore SA, Johnston RA. Obesity and asthma. Pharmacol Ther 2006;110:83–102.
26. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. Am J Respir Crit Care Med 2006;174:112–9.
27. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AWJr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112:1796–808.
28. Ingle PV, Patel DM. C-reactive protein in various disease condition–an overview. Asian J Pharm Clin Res 2011;4:9-13.
29. Barisione G, Baroffio M, Crimi E, Brusasco V. Beta-adrenergic agonists. Pharmaceuticals 2010;3:1016–44.
30. Fernandes BL, Henry JP, Goldie GR. β-Adrenoceptor agonists. Pharma and Ther of Asthma and COPD. Available from: www.springer.com. [Last accessed on 06 Nov 2016]
31. Kaur M, Holden NS, Wilson SM, Sukkar MB, Chung KF, Barnes PJ, *et al.* Effect of beta-2 adrenoceptor agonists and other cAMP-elevating agents on inflammatory gene expression in human ASM cells: a role for protein kinase A. Am J Physiol Lung Cell Mol Physiol 2008;295:L505–14.
32. Sears MR, Hamilton MB. Adverse effects of β-agonists. J Aller Clin Immunol 2002;110:322–8.

How to cite this article

Aprilita Rina Yanti Eff. The incidence of hypertension in asthma patients who treated with beta-2 agonists bronchodilators. Int J Pharm Pharm Sci 2017;9(4):181-184.

INCIDENCE OF HYPERTENSION IN ASTHMA PATIENTS WHO TREATED WITH BETA-2 AGONISTS BRONCHODILATORS

ORIGINALITY REPORT

14%	8%	10%	6%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Chi-Chen Hong, Ashley Pajak, Susan L. Teitelbaum, Nita Vangeepuram et al. "Younger pubertal age is associated with allergy and other atopic conditions in girls", Pediatric Allergy and Immunology, 2014 Publication	1%
2	Florin, Timothy H. J., Ewan W. J. Paterson, Elizabeth V. Fowler, and Graham L. Radford-Smith. "Clinically active Crohn's disease in the presence of a low C-reactive protein", Scandinavian Journal of Gastroenterology, 2006. Publication	1%
3	Hyun-Min Choi, Charles L. Stebbins, Hosung Nho, Kyung-Ae Kim, Chanho Kim, Jong-Kyung Kim. "Skeletal muscle metaboreflex is enhanced in postmenopausal women", European Journal of Applied Physiology, 2011 Publication	1%

4	Internet Source	1%
5	Rajesh Kumar. "Maternal Pre-Pregnancy Obesity and Recurrent Wheezing in Early Childhood", Pediatric Allergy Immunology and Pulmonology, 10/09/2010 Publication	1%
6	Minna Tommola, Pinja Ilmarinen, Leena E. Tuomisto, Hannu Kankaanranta. "Concern of underdiagnosing asthma–COPD overlap syndrome if age limit of 40 years for asthma is used", European Respiratory Journal, 2017 Publication	1%
7	Naim Kia, Farhad Malek, Elaheh Ghods, Mona Fathi. "Health-related quality of life of patients with asthma: a cross-sectional study in Semnan, Islamic Republic of Iran", Eliminating hepatitis from the Eastern Mediterranean Region, 2017 Publication	1%
8	L. B. Fernandes, P. J. Henry, R. G. Goldie. "Chapter 1 β-Adrenoceptor Agonists", Springer Nature, 2004 Publication	1%
9	Ayse Bilge Ozturk, Benjamin Arthur Turturice, David L. Perkins, Patricia W. Finn. "The Potential for Emerging Microbiome-Mediated Therapeutics in Asthma", Current Allergy and	1%

	Asthma Reports, 2017 Publication	
10	Submitted to University of Surrey Student Paper	1%
11	atm.amegroups.com Internet Source	<1%
12	Maged M. Yassin, Ayman M. AbuMustafa, Mohamed M. Yassin. "Serum leptin in diabetic nephropathy male patients from Gaza Strip", Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 2019 Publication	<1%
13	www.cyclingcme.com Internet Source	<1%
14	library.wur.nl Internet Source	<1%
15	Submitted to Cleveland State Community College Student Paper	<1%
16	www.onlinejacc.org Internet Source	<1%
17	Submitted to CSU, Dominguez Hills Student Paper	<1%
18	Ronald Ross Watson, Peter Rohdewald, Graciela E. Silva. "Asthma risk factors in Desert	<1%

	Southwest of USA: Role of nutritional supplement, Pycnogenol® in therapy", Journal of Nutritional & Environmental Medicine, 2009 Publication	
19	Submitted to Universität Hohenheim Student Paper	<1%
20	Shelley R. Salpeter, Thomas M. Ormiston, Edwin E. Salpeter. "Cardiovascular Effects of β-Agonists in Patients With Asthma and COPD", Chest, 2004 Publication	<1%
21	agx.abvpress.ru Internet Source	<1%
22	Submitted to Saint Leo University Student Paper	<1%
23	www.biotechnosolutions.com Internet Source	<1%
24	Anand S. Dutta. "Discovery of New Medicines", The Textbook of Pharmaceutical Medicine, 11/13/2009 Publication	<1%
25	wrap.warwick.ac.uk Internet Source	<1%
26	www.greenmedinfo.com Internet Source	<1%

27	Klaus F. Rabe, John R. Hurst, Samy Suissa. "Cardiovascular disease and COPD: dangerous liaisons?", European Respiratory Review, 2018 Publication	<1%
28	Chang, Tung-Ti, Chieh-Chen Huang, and Ching-Hsiang Hsu. "Inhibition of Mite-Induced Immunoglobulin E Synthesis, Airway Inflammation, and Hyperreactivity by Herbal Medicine STA-1", Immunopharmacology and Immunotoxicology, 2006. Publication	<1%
29	www.jofamericanscience.org Internet Source	<1%
30	Lindeman, R. D.. "SUCCESSFUL AGING", Experimental Lung Research, 2005. Publication	<1%
31	wwwnc.cdc.gov Internet Source	<1%
32	Submitted to Broward Community College Student Paper	<1%
33	journals.lww.com Internet Source	<1%
34	www.homoeopathycure.com Internet Source	<1%
35	Sangeeta Bhallamudi, Jennifer Connell,	

Christina M Pabelick, Y S Prakash, Venkatachalem Sathish. "Estrogen Receptors Differentially Regulates Intracellular Calcium Handling in Human Non-asthmatic and Asthmatic Airway Smooth Muscle Cells", American Journal of Physiology-Lung Cellular and Molecular Physiology, 2019

Publication

<1%

36 Submitted to Study Group Australia

Student Paper

<1%

37 Submitted to Victoria University

Student Paper

<1%

Exclude quotes	On	Exclude matches	< 10 words
Exclude bibliography	Off		